An oncoinformatics study to predict the inhibitory potential of recent FDA-approved anti-cancer drugs against human Polo-like kinase 1 enzyme: a step towards dual-target cancer medication

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Abstract

Cancer prevalence has increased at an alarming rate worldwide. Complexity, resistance mechanism and multiple compensatory survival pathways of cancer cells have abated the response of currently available cancer medications. Therefore, multi-target agents rather than single target might provide a better solution to these cancer therapy issues. In the present study, anti-PLK1 (Polo-like kinase 1) potential of the eight FDA-approved (2017) anti-cancer drugs have been explored using molecular docking approach. Out of all the tested drugs, brigatinib, niraparib and ribociclib showed better binding affinity towards the ‘kinase domain’ of PLK1. The Gibbs free binding energy (ΔG) and inhibition constant (K_i) values for brigatinib, niraparib and ribociclib interaction with the kinase domain of PLK1 were ‘− 8.05 kcal/mol and 1.26 μM ’, ‘− 8.35 kcal/mol and 0.729 μM ’ and ‘− 7.29 kcal/mol and 4.52 μM ’, respectively. Interestingly, the docking results of these three drugs were better than the known PLK1 inhibitors (BI-2536 and rigosertib). The ΔG and K_i values for BI-2536 and rigosertib interaction with the kinase domain of PLK1 were ‘− 6.8 kcal/mol and 10.38 μM ’ and ‘− 6.6 kcal/mol and 14.51 μM ’, respectively. Brigatinib, niraparib and ribociclib have been approved by FDA for the treatment of non-small cell lung cancer, ovarian/fallopian tube cancer and breast cancer, respectively. PLK1 is regarded as a potential cancer target, and it is specifically over-expressed in different types of cancer cells, including aforementioned cancers. Actually, the target enzymes for anti-cancer action of brigatinib, niraparib and ribociclib are tyrosine kinase, poly(ADP-ribose) polymerase and cyclin-dependent kinase 4/6, respectively. However, based on our outcomes, we could safely state that PLK1 might plausibly emerge as an add-on target for each of these three anti-cancer drugs. We strongly believe that this study would assist in the development of better dual-targeting cancer therapeutic agent in the near future.

Keywords Anticancer drugs · Dual therapy · Molecular docking · Multi-target agents · Polo-like kinase 1

Introduction

The second major reason of death around the globe is cancer. Cancer was responsible for approximately 8.8 million deaths in the year 2015, and one out of every six deaths is a direct consequence of cancer (WHO 2015). There are different factors that are involved in cancer, so therapeutic strategies against a particular target, usually remain unsuccessful (Xie and Bourne 2015; Mehta et al. 2014). In fact, targeting a single factor that has expressed in a cancer cell might lead to resistance development (Mehta et al. 2014). In addition, several different pathways assist in the survival cancer cells, and blocking one pathway might trigger the alternate compensatory pathway (Xie and Bourne 2015). Thus, a multi-target approach seems to be a promising option (Xie and

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Bourne 2015; Mehta et al. 2014; Holohan et al. 2013). In the present study, we have screened recently FDA-approved anti-cancer drugs against one, the promising cancer target, i.e., a member of Polo-like kinases (PLKs).

PLKs belong to serine–threonine kinase family that is omnipresent in different types of eukaryotic cells (Golsteyn et al. 1996). There are five members in the family of human PLKs, from PLK1 to PLK5. Among these five members, PLK1 is the most explored and best characterized (Lens et al. 2010). PLK1 regulates various functions related to cell cycle progression (Van de Weerd and Medema 2006; Glover et al. 1998), such as regulating G2/M checkpoint and entry into mitosis via triggering cdc 2/cyclinB complex, controlling segregation of chromosome, maturation of centrosome, activating anaphase advancing complex, assisting in DNA replication and inducing cytokinesis via NudC phosphorylation (Van de Weerd and Medema 2006; Sumara et al. 2002; Roshak et al. 2000; Kotani et al. 1998; Lane and Nigg 1996). Several reports have suggested that PLK1 is over-expressed in different cancerous cells such as endometrial, breast, ovarian, colorectal, head and neck squamous cell, pancreatic, lung, stomach and skin cancers (Strebhardt and Ullrich 2006; Weichert et al. 2005; Gray et al. 2004; Takahashi et al. 2003; Kneisel et al. 2002). It has been found that down-regulation of PLK1 would hinder the growth cancerous cells; however, normal cells remain unaffected (Liu et al. 2006). Thus, PLK1 could be considered as a promising target for the treatment of cancer (Liu et al. 2017). In the year 2017, we have extensively studied enzinformatics and molecular aspects of PLK1 targeting for the treatment of cancer. We found that most of the known PLK1 inhibitors interact with L59, C133 and F183 amino acid residues of the ‘kinase domain’ of PLK1 enzyme (Shakil et al. 2017). Earlier in the year 2014, we have studied the

anti-PLK1 potential of components of plant extract using ‘kinase domain’ of PLK1 enzyme as a target (Rizvi et al. 2014). These results prompted us to explore recent FDA-approved anticancer drugs for their anti-PLK1 potential. Our main purpose was to observe the dual-target potential of these recently approved anti-cancer drugs.

We have picked eight drugs that are approved in the year 2017 by FDA. Out of these eight, six (abemaciclib, brigatinib, copanlisib, midostaurin, neratinib and ribociclib) are kinase inhibitors, one (enasidenib) is isocitrate dehydrogenase 2 inhibitor and one (niraparib) is poly(ADP-ribose) polymerase inhibitor (FDA 2017). Table 1 summarizes the targeted cancer and enzyme for each of these anti-cancer drugs.

PLK1 over-expression was seen in all sorts of cancers that are mentioned in Table 1 (Liu et al. 2017). In this study, anti-cancer drugs mentioned in Table 1 were used as ligands for targeting PLK1 to pick the most potent inhibitor out of eight drugs; however, two established PLK1 inhibitors BI-2536 and rigosertib were taken as controls for the comparative analysis (Liu et al. 2017; Steegmaier 2007; Gumireddy 2005). This study would propose the strong PLK1 inhibitor out of eight recently approved anti-cancer drugs that might become a part of plausible future multi-target cancer therapy.

At this point of time, Protein Data Bank has no crystal structure to assist the study of interaction between these anti-cancer drugs and PLK1. Thus, exploring anti-PLK1 ability of these drugs would provide an additional advantage to current cancer therapy regime. Moreover, the present study was the preliminary investigational step towards reconsideration of single target anti-cancer drugs as multi-target drugs. Even though a lot of researches are still needed to establish strong and effective multi-target anti-cancer drugs, it is our firm belief that the

Table 1 Target enzymes for FDA (2017)-approved anti-cancer drugs

Name of the drug	FDA approval	Type of cancer	Target enzyme
Verzenio (abemaciclib)	September 2017	HER2-breast cancer	Cyclin-dependent kinases 4 and 6 (CDK4 and CDK6)
Alunbrig (brigatinib)	April 2017	Non-small cell lung cancer	Multiple Kinases (potent tyrosine kinase inhibitor)/ALK and ALK-mediated phosphorylation
Aliqopa (copanlisib)	September 2017	Follicular lymphoma	PI3K-alpha and PI3K-delta isoforms
Rydapt (midostaurin)	April 2017	FLT3-positive acute myeloid leukemia	Multiple receptor tyrosine kinases
Nerlynx (neratinib)	July 2017	HER2 breast cancer	Kinase inhibitor that irreversibly binds to epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2). Reduces EGFR and HER2 autophosphorylation
Kisqali (ribociclib)	March 2017	Breast cancer	Cyclin-dependent kinases (CDK) 4 and 6
IDHIFA (enasidenib)	August 2017	Acute myeloid leukemia with IDH2 mutation	Isocitrate dehydrogenase 2
ZeJula (niraparib)	March 2017	Recurrent epithelial ovarian and fallopian tube cancer	Poly(ADP-ribose) polymerase (PARP)

present study would be valuable for the researchers involved in drug designing of more strong and adaptable PLK1 inhibitors.

Methodology

To predict the inhibitory potential and interaction of recently (2017) FDA-approved anti-cancer drugs (abemaciclib, brigatinib, copanlisib, midostaurin, neratinib, ribociclib, enasidenib and niraparib) with PLK1 enzyme, molecular docking analysis with PLK1 'kinase domain' was performed using the method of Rizvi et al. (2013). Protein Data Bank was used to obtain the crystal structure of PLK1 (PDB ID: 2OWB) solved at 2.1-Å resolutions, whereas, PubChem database was used to obtain pdb structures of abemaciclib (PubChem CID: 46220502), brigatinib (PubChem CID: 68165256), copanlisib (PubChem CID: 24989044), midostaurin (PubChem CID: 9829523), neratinib (PubChem CID: 9915743), ribociclib (PubChem CID: 44631912), enasidenib (PubChem CID: 89683805) and niraparib (PubChem CID: 24958200). In addition, structures of established PLK1 inhibitors BI-2536 (PubChem CID: 11364421) and rigosertib (PubChem CID: 6918736) as positive controls were also taken from PubChem. After that, 'Auto dock 4.2' was used to dock each drug/ligand (including control) with the kinase domain of PLK1 enzyme individually. For each ligand, we have added Gasteiger partial charges and minimize its energy using MMFF94 force field. Nonpolar hydrogen atoms were merged and rotatable bonds were appropriately defined. Protein model was used to carry out docking calculations. Solvation parameters, Kollman united atom-type charges and hydrogen atoms were added with the help of AutoDock. Grid box dimension was set as 40 Å × 40 Å × 40 Å along with spacing of 0.375 Å using 'Auto Grid' that was aimed towards the kinase domain of PLK1 enzyme. To target specifically towards the 'ATP-binding site' or 'kinase domain' of PLK1 enzyme, we kept *x*, *y*, and *z* coordinate values as 0.069, 23.58 and 66.741, respectively. For the van der Waals and the electrostatic term calculation, we applied the default parameters and dielectric functions present in the 'Auto Dock' program. For docking simulations, 'Solis and Wets local search method' and 'Lamarckian genetic algorithm' were used. Initial position, orientation and torsions of the drug/ligand were set arbitrarily. For each docking, 100 runs were applied. Every docking run ended after the 2,500,000 energy evaluation with population size 150. The final figures were generated using Discovery Studio2.5 (Accelrys).

Results and discussion

Cancer is a complex disease that includes the association of various pathophysiological factors (Padma 2015). Unfortunately, the cases of cancer are increasing at an alarming rate and it has become one of the prominent reasons of death all

over the world (Padma 2015; WHO 2015; Jemal et al. 2011). Chemotherapy is considered as one of the main strategy for the cancer treatment. However, they often become ineffective due to their general toxicity and incompetence to differentiate between normal and cancerous cell; furthermore, the ability of cancer cell to develop resistance reduces the effect of a target specific drug (Xu and McLeod 2001). Cancer cells have the ability to acclimatize to the adverse circumstances using different molecular and cellular mechanisms (Xie and Bourne 2015; Holohan et al. 2013). In fact, survival of cancer cell has been simultaneously supported by several mechanisms; thus, switching off one pathway might activate the alternate compensatory pathway (Xie and Bourne 2015). Hence, new standardized strategies of combination therapies have been planned to cope up with these drug resistance pathways (Wang et al. 2015; Crystal et al. 2014; Holohan et al. 2013). Interestingly, multi-target or dual-target drugs have gained noticeable recognition over the last few years, to control diseases with multifarious etiology and to overcome drug resistance (Koeberle and Werz 2014; Zheng et al. 2014; Li et al. 2014; Talevi et al. 2012). In the present study, the inhibitory potential of recent (2017) FDA-approved anti-cancer drugs have been tested against Polo-like kinase 1 (PLK1) enzyme. The main reason to select PLK1 was its over-expression in various cancer cells and targeting PLK1 would retard the growth of cancerous cells without affecting the normal cell growth (Liu et al. 2006; Strebhardt and Ullrich 2006; Weichert et al. 2005; Gray et al. 2004; Takahashi et al. 2003; Kneisel et al. 2002). Thus, exploration of anti-cancer drugs for other target such as PLK1 might lead to the selection and establishment of better dual-target therapy for the cancer treatment in near future.

The molecular docking results showed that out of eight anti-cancer drugs, three drugs, i.e., brigatinib, niraparib and ribociclib, showed better interaction than the control (BI-2536 and rigosertib). Brigatinib has been stated as a wonder drug by Bedi et al. (2018) for the treatment of ALK-positive non-small cell lung cancer. It is basically an inhibitor of tyrosine kinase that can inhibit the activity of other kinases such as ROS1, EGFR and insulin-like growth factor-1 receptor. Interestingly, brigatinib can rectify the drug resistance issues of alectinib, crizotinib and ceritinib in ALK-positive non-small cell lung cancer. In addition, brigatinib is safer than the other anti-cancer medications available for the treatment of ALK-positive non-small cell lung cancer (Bedi et al. 2018; Gettinger et al. 2016). In our study, the docking analysis demonstrated that brigatinib was docked into the kinase domain cavity between N terminal R57 and C terminal D194 (Fig. 1). Brigatinib interacted with PLK1 "kinase domain" through 19 amino acid residues, namely R57, L59, G60, K61, G62, A65, K66, C67, A80, K82, V114, L130, E131, L132, C133, R134, R136, F183 and D194 (Table 2). However, Gibbs free binding

energy (ΔG) and inhibition constant (K_i) values were found to be -8.05 kcal/mol and 1.26 μ M, respectively. Here, C133 amino acid residue of PLK1 kinase domain showed hydrogen bonding with brigatinib, while, R134 interacted with one oxygen atom O_2 of brigatinib via the polar bond. The total intermolecular energy of “PLK1–brigatinib” docking was observed as -9.35 kcal/mol. “Electrostatic” energy component was $+1.43$ kcal/mol, whereas, “van der Waals,” “hydrogen bond,” and “desolvation” energy components collectively found to be as -10.78 kcal/mol. Total interacting surface area for PLK1–brigatinib interaction was observed as 828.039 $\text{\AA}^2$.

Fig. 1 Docking interaction of brigatinib with PLK1 enzyme ‘kinase’ domain. The stick representation was used for displaying ligand ‘brigatinib’

Niraparib is a potent inhibitor of poly(ADP-ribose) polymerase (PARP). It has been approved by FDA as a medication for ovarian cancer patients who possess no somatic mutation in the breast cancer (BRCA) gene. In general, niraparib is very much tolerable and its toxicities could be managed easily (Essel and Moore 2018). Interestingly, niraparib is the first PARP inhibitor that has shown effectiveness against recurrent ovarian and fallopian tube cancer. In addition, niraparib is used as a maintenance therapy for the cancer that has fully or partially responded to platinum-based chemotherapy (Mirza et al. 2016). Out of all anti-cancer drugs tested in the present study, niraparib was found to be the most potent inhibitor of PLK1 ‘ATP-binding or kinase’ domain. Niraparib interacted to PLK1 ‘kinase domain’ through 11 amino acid residues, i.e., R57, L59, A80, V114, L130, E131, L132, C133, R134, R136 and F183 (Fig. 2; Table 2). The ΔG and K_i values for ‘niraparib-PLK1’ interaction were estimated as -8.35 kcal/mol and 0.729 μ M, respectively. Two amino acid residues, namely L59 and E131, of enzyme PLK1 showed hydrogen bonding with niraparib, while R136 amino acid of PLK1 showed polar bonding with niraparib. Some hydrophobic interactions were observed between three carbon atoms (CG1, CG2 and CD1) and amino acid residues (V114, L130 and L132) of ‘kinase domain’ of PLK1 enzyme. Simultaneously, π – π stacking of F183 with two carbon atoms (CD2 and CE2) of niraparib was also observed to augment the affinity of niraparib with PLK1 enzyme. These results were similar to our earlier study where the most potent plant-isolated compound (1,4-cyclohexylphenyl)ethanone showed a similar type of interaction with F183, R136, V114 and L132 amino acid residues of PLK1 (Rizvi et al. 2014). In the year 2012, Han et al. while studying the interaction of beta-carboline with PLK1 enzyme found that π – π stacking with benzene at p-fluorobenzyloxy group played an important role in docking. Lu et al. (2011) have also shown that F183 amino acid residue of PLK1 interacted with one of the screened compound

Table 2 Amino acid residues of ‘kinase domain’ of PLK1 involved in the interaction of different FDA (2017) approved anti-cancer drugs

Anti-cancer drugs (ligands)	Interacting amino acids of ‘kinase domain’ of PLK1
Abemaciclib	L59, G60, K61, G62, C67, A80, K82, V114, L130, E131, L132, C133, R136, E140, F183, D194
Brigatinib	R57, L59, G60, K61, G62, A65, K66, C67, A80, K82, V114, L130, E131, L132, C133, R134, R136, F183, D194
Copanlisib	F58, L59, G60, G62, C67, A80, K82, E131, L132, C133, R136, F183, D194
Midostaurin	L59, G60, K61, G62, C67, A80, K82, L130, R136, G180, F183, D194
Neratinib	R57, F58, L59, G60, K61, C67, E69, A80, L130, C133, R134, R136, F183
Ribociclib	L59, G60, C67, A80, K82, L130, E131, C133, R136, F183, D194
Enasidenib	L59, G60, K61, G62, C67, A80, K82, V114, L130, E131, L132, C133, F183, G193, D194
Niraparib	R57, L59, A80, V114, L130, E131, L132, C133, R134, R136, F183
Control1 BI-2536	F58, L59, K61, G62, A65, C67, A80, K82, L130, C133, R136, F183, D194
Control2 Rigosertib	L59, G60, K61, G62, A65, K66, C67, E69, K82, L130, C133, R134, R136, F183, D194

Fig. 2 Docking interaction of niraparib with PLK1 enzyme ‘kinase’ domain. The stick representation was used for displaying ligand ‘niraparib’

[73] via stacking with aromatic ring, which showed a significant influence on the conformational equilibrium of the entire compound. However, the total intermolecular energy of ‘PLK1–niraparib’ interaction in our study was observed as -8.66 kcal/mol, whereas, total “van der Waals,” “hydrogen bond,” and “desolvation” energy were found to be as -8.57 kcal/mol with “electrostatic” energy as -0.08 kcal/mol. Total interacting surface area for ‘PLK1–niraparib’ interaction was estimated to be $800.984 \text{ \AA}^2$.

Ribociclib is used together with endocrine therapy for the treatment of hormone receptor (HR)+, human epidermal growth factor receptor 2 (HER2)– in advanced breast cancer. It is in fact a potent inhibitor of cyclin-dependent kinase 4/6 (CDK4/6) and inhibition of CDK4/6 is considered as a plausible therapeutic strategy for HR+ metastatic breast cancer patients (Burris 2018; Shah et al. 2018). Even though ribociclib seems to be an effective anti-cancer medication, it has certain manageable side effects that have been observed in 20% or more patients, such as nausea, neutropenia, fatigue, leucopenia, vomiting, constipation, back pain, alopecia and headache (Shah et al. 2018). In the present study, ribociclib interaction with the kinase domain of PLK1 showed ΔG and K_i values as -7.29 kcal/mol and $4.52 \text{ \mu M}$, respectively.

Fig. 3 Docking interaction of ribociclib with PLK1 enzyme ‘kinase’ domain. The stick representation was used for displaying ligand ‘ribociclib’

Eleven amino acid residues (L59, G60, C67, A80, K82, L130, E131, C133, R136, F183, D194) of PLK1 ‘kinase or ATP-binding’ domain were found to be involved in interaction with ribociclib (Fig. 3; Table 2). Hydrogen bonding was observed between ribociclib and C133 amino acid residue of PLK1 enzyme, whereas, L59 was involved in hydrophobic interaction with one of the carbon atom (CD2) of ribociclib. Further, the total intermolecular energy of ‘ribociclib–PLK1’ interaction was observed as -7.58 kcal/mol, whereas, “van der Waals,” “hydrogen bond,” and “desolvation” energy collectively were found to be as -8.44 kcal/mol along with “electrostatic” energy as $+0.86$ kcal/mol. Total interacting surface area for ‘PLK1–ribociclib’ interaction was estimated to be $925.76 \text{ \AA}^2$.

Other drugs that we have tested against PLK1 were midostaurin, abemaciclib, enasidenib, copanlisib and neratinib. Midostaurin is basically a fms-like tyrosine kinase 3 (FLT-3) inhibitor that was approved by FDA for the treatment of *FLT3*-mutant acute myeloid leukemia (Stone et al. 2018; Levis 2017). The ΔG and K_i values for ‘PLK1–Midostaurin’ interaction were -6.75 kcal/mol and $11.32 \text{ \mu M}$, respectively, and 12 amino acids (L59, G60, K61, G62, C67, A80, K82, L130, R136, G180, F183, D194) of PLK1 ‘kinase

domain' were found to interact with midostaurin (Fig. 4; Table 2). Here, R136 and K82 amino acid residues of PLK1 were found to interact with midostaurin via hydrogen bonding. Abemaciclib is another CDK4/6 inhibitor like ribociclib that is active against HR+ and HER- breast cancer cells (Kotake and Toi 2018; Goetz et al. 2017). In the present study, abemaciclib interaction with PLK1 enzyme showed ' ΔG and K_i ' as -6.31 kcal/mol and 23.88 μ M, respectively. Sixteen amino acid residues (L59, G60, K61, G62, C67, A80, K82, V114, L130, E131, L132, C133, R136, E140, F183, D194) of PLK1 enzyme were involved in the interaction of abemaciclib (Fig. 5; Table 2). Amino acid residues, C133 and F183, of PLK1 enzyme were involved in hydrogen bonding and π - π stacking, respectively.

Enasidenib has also shown some decent interaction with 15 amino acid residues of PLK1 (Fig. 6; Table 2) and ' ΔG and K_i ' for this interaction were observed as -6.04 kcal/mol and 37.35 μ M, respectively. In fact, enasidenib is an inhibitor of mutant isocitrate dehydrogenase-2 enzyme that has been approved for the treatment of acute myeloid leukemia with IDH2 mutation (Dugan and Pollyea 2018; Stein et al. 2017). On the other hand, *copanlisib* showed ' ΔG and K_i ' for its docking with PLK1 as -5.06 kcal/mol and 196.39 μ M, respectively, and 13 amino acid residues were involved in its interaction with PLK1 (Fig. 7; Table 2). Copanlisib is an inhibitor of phosphatidylinositol 3-kinase and approved for the treatment of follicular lymphoma (Dreyling et al. 2017). Amongst the eight anticancer drugs tested, the least active against PLK1 enzyme was neratinib with ΔG and K_i values as -1.77 kcal/mol and 50.68 mM, respectively; however, 13 amino acids of PLK1 interacted with it (Fig. 8; Table 2).

Fig. 4 Docking interaction of midostaurin with PLK1 enzyme 'kinase' domain. The stick representation was used for displaying ligand 'midostaurin'

Fig. 5 Docking interaction of abemaciclib with PLK1 enzyme 'kinase' domain. The stick representation was used for displaying ligand 'abemaciclib'

Neratinib has been approved for HER2-positive breast cancer treatment (Echavarria et al. 2017) but did not appear to be a potent inhibitor of PLK1.

Fig. 6 Docking interaction of enasidenib with PLK1 enzyme 'kinase' domain. The stick representation was used for displaying ligand 'enasidenib'

Fig. 7 Docking interaction of copanlisib with PLK1 enzyme 'kinase' domain. The stick representation was used for displaying ligand 'copanlisib'

Fig. 8 Docking interaction of neratinib with PLK1 enzyme 'kinase' domain. The stick representation was used for displaying ligand 'neratinib'

It is noteworthy to mention that recently our research team has conducted a thorough analysis of the kinase domain of PLK1 enzyme via using several known and established PLK1 inhibitors (Shakil et al. 2017). Shakil et al. (2017) found that 'volasertib' which is considered as a breakthrough therapy showed binding with PLK1 through six important amino acid residues of the kinase domain, i.e., L59, C67, L130, C133, R136 and F183. In the present study, known inhibitors BI-2536 and rigosertib interacted with PLK1 with 13 amino acid residues (F58, L59, K61, G62, A65, C67, A80, K82, L130, C133, R136, F183, D194) (Fig. 9; Table 2) and 15 amino acid residues (L59, G60, K61, G62, A65, K66, C67, E69, K82, L130, C133, R134, R136, F183, D194) (Fig. 10; Table 2), respectively. In addition, ΔG and K_i values for 'BI-2536-PLK1' and 'rigosertib-PLK1' interactions were found to be as -6.8 kcal/mol and 10.38 μM and -6.6 kcal/mol and 14.51 μM , respectively. The PLK1 interaction results of tested anti-cancer drugs when compared with BI-2536 and rigosertib (known PLK1 inhibitors) showed that brigatinib, niraparib and ribociclib were bounded more efficiently towards the 'kinase or ATP-binding domain' of PLK1 enzyme than the known PLK1 inhibitors. ΔG values of 'brigatinib-PLK1', 'niraparib-PLK1' and 'ribociclib-PLK1' interactions were -8.05 , -8.35 and -7.29 kcal/mol, respectively; in contrast, ΔG values of 'BI-2536-PLK1' and 'rigosertib-PLK1' interactions were -6.8 and -6.6 kcal/mol, respectively. Interestingly, five amino

Fig. 9 Docking interaction of BI-2536 with PLK1 enzyme 'kinase' domain. The stick representation was used for displaying ligand 'BI-2536'

Fig. 10 Docking interaction of rigosertib with PLK1 enzyme 'kinase' domain. The stick representation was used for displaying ligand 'rigosertib'

acid residues, namely L59, L130, C133, R136, and F183, of PLK1 'kinase domain' could be observed as common in inhibitors (including volasertib) as well as the three potential anti-cancer drugs. It has been a well established fact that the protein–ligand interaction is only feasible when the Gibbs free energy (ΔG) change of the system is negative, and more negative free energy corresponds to better affinity (Du et al. 2016). Thus, even though some of these amino acids were common in the interaction of all the tested anti-cancer drugs with PLK1 enzyme, the ΔG and K_i results prompted us to select only brigatinib, niraparib and ribociclib. However, further validations of the obtained results are warranted via in vitro and in vivo analysis of these selected drugs. Nevertheless, we could safely state that brigatinib, niraparib and ribociclib possess the potential to become a part of dual or multi-target anti-cancer therapy. In fact, development of multi-target agents for the treatment of cancer seems to be a promising approach (Talevi 2015; Xie and Bourne 2015; Mehta et al. 2014). Multi-target approach could be achieved by applying combination therapy instead of developing multi-target or dual-target agents. Still, multi-target agents have certain advantages over such combination therapy such as less chances of drug interactions, better patient compliance and importantly, the easy pharmacokinetics prediction (Talevi 2015). Therefore, the information obtained from the present study might act as a basis for the development of future dual-targeting anti-cancer agents in the form of brigatinib targeting 'tyrosine kinase and PLK1', niraparib targeting 'PARP and PLK1' and ribociclib targeting 'CDK4/6 and PLK1'. Hence, the addition of PLK1, a cancer target that is found to be specifically over-expressed in numerous cancers (Liu et al. 2006; Strebhardt and Ullrich 2006; Weichert et al.

2005; Gray et al. 2004; Takahashi et al. 2003; Kneisel et al. 2002), might boost the anti-cancer therapy regime in the near future.

Conclusion

Therapeutic management of cancer has not yet been accomplished completely due to resistant and complex nature of cancer cells. In fact, cancer cells follow alternate compensatory pathways when a single targeted drug is used for the treatment. Hence, applying multi-targeted approach appears to be beneficial for cancer therapy. We have explored the dual-targeting potential of the eight FDA-approved (2017) cancer drugs by targeting them on PLK1 enzyme. PLK1 is over-expressed specifically in different types of cancer cells and its inhibition would certainly provide an add-on advantage. The molecular docking results predicted that out of all the drugs tested, brigatinib, niraparib and ribociclib showed better binding affinity towards the 'kinase' domain of PLK1. In terms of ΔG and K_i values, brigatinib, niraparib and ribociclib were found to be even more competent than known PLK1 inhibitors (rigosertib and BI-2536). Further, in vitro and in vivo analyses are required to validate these outcomes. However, it is a fact that in silico outcomes usually corresponds well with the wet lab results. Thus, we could safely state that such information might aid in the development of better dual-targeting cancer therapeutic agent in the near future.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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